AXCAN PHARMA™

Axcan Scandipharm Inc.
22 Inverness Center Parkway
Birmingham, Alabama 35242 USA

Tel.: (205) 991-8085
1-800-615-4393
Fax: (205) 991-0639

www.axcan.com

Sept. 28, 2007

Dockets Management Branch, HFA-305
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2007D-0168: May 31, 2007 (72 FR 30386-30388)
Draft Guidance on Mesalamine

Dear Sir/Madam:

Axcan Scandipharm Inc. (Axcan) is submitting the following comments on the FDA's proposed guidance entitled, "Draft Guidance on Mesalamine" (May 2007). This product-specific guidance was published in conjunction with the general draft guidance "Guidance for Industry - Bioequivalence Requirements for Specific Products".

Axcan is a leading specialty pharmaceutical company that develops and markets a wide range of products to treat gastrointestinal diseases (GI) and disorders, such as inflammatory bowel disease, cholestatic liver diseases, irritable bowel syndrome, and complications related to pancreatic insufficiency. Axcan's mission is to improve the quality of care and health of patients suffering from gastrointestinal diseases and disorders by providing effective therapies for patients and their specialized caregivers.

Axcan supports FDA's efforts to develop product-specific guidance describing data required to support Abbreviated New Drug Applications (ANDAs). This initiative will ultimately protect the public health by ensuring consistency in the way generic drug development is conducted. This enhanced clarity and transparency is of benefit to all stakeholders, including those developing both innovative and generic products.

The initiative for mesalamine rectal suppositories is particularly important due to the drug's mode of action and site of delivery. As the developer of multiple mesalamine formulations that are used to treat a range of important GI diseases, Axcan is uniquely situated to understand the distinctive properties of these products. Upon review of the FDA's recommendations for the approval of a generic mesalamine suppository, Axcan agrees with the general principles implied by the proposed studies – namely, that due to the local action of the product, conventional pharmacokinetic studies are not sufficient to establish bioequivalence. At the same time, we believe certain aspects of the draft

guidance raise concerns that should be carefully considered before the guidance is finalized.

Below, we have provided comments to each component of the proposed requirements.

1. COMMENTS ON FDA'S FIRST PROPOSED REQUIREMENT

First FDA Recommended Study	
Type of study:	Bioequivalence study with clinical endpoints
Design:	Parallel design, three arm (test, reference and placebo) in-vivo
Strengths:	500 mg and 1000 mg
Subjects:	Patients with ulcerative proctitis
Additional Comments:	Please submit a protocol to the Clinical Review Team for recommendations on study design.

1.1 Need for Clinical Endpoints

Axcan is in agreement with the FDA's recommendation for a study with clinical endpoints to support bioequivalence of a generic mesalamine suppository product with the Reference Listed Drug (RLD). Due to the local action of mesalamine suppositories in the treatment of ulcerative proctitis (UP), a conventional evaluation of serum levels is not sufficient to establish that two products are therapeutically equivalent.

As we have argued elsewhere[1], there are several reasons why clinical efficacy measurements are required, and why measurement of serum mesalamine levels alone should not be used as a measure of therapeutic equivalence for mesalamine rectal suppositories. These reasons are listed here and discussed in further detail below:

- Mesalamine acts topically within the GI tract (see Section 1.1.1 below).
    - Bioavailability is variable and low, and serum levels do not correlate with efficacy.
    - Local tissue levels of mesalamine are directly correlated with efficacy when mesalamine is administered rectally.
- Bioavailability of mesalamine from rectal suppositories is different in disease-active patients *versus* patients in remission or healthy volunteers. Bioavailability decreases as healing of the mucosa progresses. The bioavailability of mesalamine

[1] Citizen Petition, Docket 2007P-0302 "Require all manufacturers of a generic verision of CANASA (mesalamine) rectal suppositories to perform an adequate and well-controlled clinical safety and effectiveness trial".

in patients in remission tends to be similar to that in healthy volunteers (see Section 1.1.2 below).

- Limited distribution of drug product within the defined space of the rectum could increase the influence of excipients on local activity of the active pharmaceutical ingredient. Such potential local influence on efficacy would unlikely be reflected in systemic mesalamine levels (see Section 1.1.3 below).

1.1.1 Topical mesalamine is a locally acting drug

Topical mesalamine is a locally acting drug, and therefore systemic blood serum concentrations for mesalamine are an inadequate surrogate for determining therapeutic equivalence at the site of action. Both clinical and *in vitro* analyses have shown that the local concentrations of mesalamine in the rectal mucosa are the most relevant to clinical effectiveness.

Early observations with the pro-drug sulfasalazine suggested the importance of local concentrations of mesalamine to activity in the treatment of ulcerative colitis (UC) and UP (Christensen, 2000), as sulfasalzine is also poorly absorbed (3-12%) after oral administration (Klotz, 1985). Its activity was shown to be due to the active metabolite 5-ASA (mesalamine), which is largely formed by bacterial azo-reduction in the colon (Klotz, 1985). This early evidence pointed to the importance of local concentrations of mesalamine to clinical activity and, since that time, all formulations of mesalamine have been developed with the goal of delivering maximum levels to the diseased tissue.

Frieri and colleagues tested the hypothesis that the effectiveness of mesalamine is related to its mucosal concentrations by comparing disease activity with drug levels in mucosal samples obtained from UC patients (Frieri *et al.*, 2000). The 21 patients evaluated in this study were all receiving oral mesalamine formulations (2.4-3.2 g/day), with 4 patients also receiving topical treatment (2 g/day). The extent of disease was assessed through clinical, endoscopic and histological evaluations. Patients with slight endoscopic lesions had significantly ($P = 0.03$) higher mucosal mesalamine levels than those patients with a moderate endoscopic disease score. Thus, direct measurement of mesalamine in mucosal cells supports the hypothesis that local concentrations are most relevant to drug effectiveness. These findings indicate that the dose related effect of mesalamine likely depend on the concentration in the actual mucosa as opposed to serum levels.

In a parallel study, the same research team showed that mucosal mesalamine concentrations are higher when patients receive rectal administration of mesalamine in addition to oral therapy. Twenty-two (22) patients with UC were randomized to receive either 2.4 g/day of oral mesalamine ($n = 11$) or 2.4 g/day of oral mesalamine plus 4 g/day of topical mesalamine ($n = 11$). Endoscopic biopsies were taken from both the rectum and descending colon after 2 weeks of treatment, and analyzed for tissue mesalamine levels. Mucosal levels of mesalamine were found to be significantly higher in patients receiving the combination therapy. In rectal samples, the median values of mucosal mesalamine concentration were 52.1 ng/mg in the combination group *versus* 0.2 ng/mg in

patients receiving only oral therapy (P<0.0001). In samples from the descending colon, the median values of mesalamine concentration were 15.9 ng/mg in oral therapy patients *versus* 46.6 ng/mg in the combination group (P<0.01) (Frieri *et al.*, 1999).

The increased local concentrations of mesalamine may be responsible for enhanced clinical effectiveness with combination therapy (oral plus rectal). Clinical trials as well as a meta-analysis have demonstrated that concomitant therapy is better than oral therapy alone in the treatment of UC and UP (Cohen *et al.*, 2000; d'Albasio *et al.*, 1997; Safdi *et al.*, 1997), despite relatively low blood levels of mesalamine from rectal enemas and suppositories (Bondesen *et al.*, 1988; Campieri *et al.*, 1985; Jacobsen *et al.*, 1991; Norlander *et al.*, 1989).

A randomized, double-blind clinical trial was conducted to compare oral, rectal and combination therapy in the treatment of distal UC (Safdi *et al.*, 1997). Sixty (60) outpatients with UC were randomized to receive either a 4 g mesalamine rectal enema once nightly (n = 18), oral mesalamine tablets 2.4 g/day (n = 22), or a combination of both treatments (n = 20) for 6 weeks. The combination therapy resulted in a greater improvement in the disease activity index (DAI) than either treatment alone. Similarly, d'Albasio and colleagues showed that a combination of oral mesalamine tablets with a rectal enema was more effective in prevention of relapse in patients with UC than oral treatment alone (d'Albasio *et al.*, 1997).

In 2000, Cohen and colleagues published a meta-analysis and overview of treatment options for left-sided UC (L-UC) and UP. After evaluating 67 trials for patients with L-UC, the authors conclude that mesalamine enemas were 10-20% more effective than oral mesalamine in the treatment of distal UC, with a progressive, dose-independent increase in remission rates with continued use of topical treatment. There were fewer available studies in UP (18 trials), but results also confirmed clinical improvement from mesalamine suppository treatment in a non-dose related manner over the 0.5 to 1.5 g / day range. The number of daily administrations has not been taken into account in the analysis. This meta-analysis suggests that drug delivery by topical methods is more efficacious than oral therapies in the treatment of these diseases (Cohen *et al.*, 2000).

Overall, clinical data support the thesis that delivering mesalamine locally to the affected area of the GI tract is an important contributor to efficacy, and are consistent with the relationship observed between mucosal mesalamine levels and enhanced clinical outcomes.

1.1.2 Systemic availability of mesalamine from suppositories is different in patients compared to healthy volunteers

In two studies reported by Aumais and coworkers, the pharmacokinetics of mesalamine after administration of suppositories was evaluated in healthy volunteers and in patients with UP (Aumais *et al.*, 2003). The results of these studies demonstrate that the absorption of mesalamine was very different in healthy volunteers and patients in remission compared to patients with active disease.

In the first group, sixteen (16) male healthy volunteers were given a single CANASA® (mesalamine) 500 mg suppository. Blood samples were collected hourly for 12 hours, and urine was collected up to 24 hours post treatment. Urine was collected over the following intervals: 0-4, 4-8, 8-12 and 12-24 hours. Twenty-four (24) hours after the single dose administration, the healthy volunteers were then given 500 mg every 8 hours for 5 days. Blood and urine were again collected after the last dose using the same scheduling. Rectal biopsies were taken 8 hours after the last dose.

In the second group, six (6) women and three (3) men with active mild to moderate UP were given a single CANASA® (mesalamine) 500 mg suppository. Blood samples were collected hourly for 12 hours and then at 18, 24 and 30 hours after the dose. Urine was collected over the following intervals: 0-4, 4-8, 8-12, 12-24 and 24-30 hours. Forty-eight (48) hours after the single dose administration, the patients received 500 mg every 8 hours for 5 days and blood and urine were again collected after the last dose using the same scheduling. Rectal biopsies were taken 8 hours after the last dose.

After a single administration of a 500 mg CANASA® suppository, the mean relative systemic bioavailability of mesalamine in UP patients (35%) was determined to be significantly higher that in healthy volunteers (14%) ($P = 0.0145$). This was reflected in C_{max} levels and AUC values that were also approximately double those in healthy volunteers (Table 1).

Table 1: Comparison of pharmacokinetics and tissue concentration for mesalamine in UP patients and healthy volunteers receiving CANASA® suppositories (Aumais *et al*., 2003)

Parameter	Single Dose (1 x 500 mg) Mean (SD)			Multiple dose (500 mg TID for 5 days) Mean (SD)		
	UP Patients (n = 9)	Healthy volunteers (n = 16)	*P*	UP Patients (n = 9)	Healthy volunteers (n = 16)	*P*
C_{max} (ng/mL)	352.9 (195.8)	192.7 (102.8)	0.012	361.1 (240.8)	359.4 (166.3)	0.983
$AUC_{0-\infty}$ (ng.h/mL)	4185.24 (2551.4)	1697.69 (1634.5)	0.009	2455.71 (1548.16)	1789.45 (1214.76)	0.245
T_{max} (h)	6.0 (3.2)	2.3 (1.4)	<0.0001	5.9 (3.5)	2.0 (1.6)	0.001
Bioavailability (%)	35% (28%)	14% (12%)	0.0145	ND	ND	ND
Tissue mesalamine (ng/mg)	ND	ND	ND	167.8 (220.6)	22.3 (39.9)	0.016

ND - Not Determined

After multiple doses of CANASA® suppositories (500 mg every 8 hours for 5 days), the difference between patients and healthy volunteers was reduced, such that there were no longer statistically significant differences in C_{max} and AUC between the groups. However, T_{max} was still significantly higher in UP patients *versus* healthy volunteers.

The reasons for the difference between healthy volunteers and patients are not confirmed but many explanations may be proposed. It has been hypothesized that, in UP, the diseased rectum may exhibit greater leakiness and be more permeable to mesalamine, which may provide for greater absorption of the drug into the systemic circulation (Aumais *et al.*, 2003). Another hypothesis is that the P-glycoprotein (P-gp) responsible for Phase 0 metabolism (cellular efflux) and usually present on the mucosa of the gut is absent in patients with ulcerated mucosa, therefore resulting in increased absorption of the drug (Dietrich *et al.*, 2003). As the mucosa heals, the levels of P-gp return to normal, reducing the absorption. Whatever the cause, the effect appears to diminish after multiple doses, because C_{max} and AUC are similar in the two populations at steady state. This is likely due to mesalamine-induced healing of the mucosa over time (Aumais *et al.*, 2003). In addition, analysis of mucosal mesalamine concentrations showed that levels were also significantly higher in UP patients in remission (mean 167.8 ng/mg) than in healthy volunteers (mean 22.3 ng/mg) ($P = 0.016$) (Aumais *et al.*, 2003).

These findings are consistent with previous conclusions (Frieri *et al.*, 2000) indicating that serum levels are not related to mucosal concentrations and hence are not predictive of the clinical effectiveness of the drug. Evidence from these experiments highlights the importance of understanding pharmacokinetics in patients in order to assess potential drug exposure. It also highlights the complications in extrapolating between serum mesalamine levels and clinical activity. Ultimately, the only method to ensure that two mesalamine suppository drug products are the same is to compare their clinical effectiveness in patients.

1.1.3 Drug product excipients could influence local activity

When given as a suppository, mesalamine is confined to the lower rectum or adjacent sigmoid colon (Williams *et al.*, 1987). Due to the relatively low volume into which the mesalamine is dispersed, and the close proximity of the dosage form to the site of action, local diffusion of the mesalamine and contact with the rectal epithelia may be influenced by excipients in the drug product. It is improbable that such potential localized formulation effects would be captured through evaluation of mesalamine serum levels in a standard pharmacokinetic study. In addition, it is unknown if any potential effect of excipients would be the same in healthy volunteers *versus* patients. Although such potential local effects cannot be stated conclusively, they reinforce the need to evaluate effectiveness by using clinical endpoints that take into account the behavior of the suppository in patients with UP.

1.2 Need for a Placebo Group

While Axcan agrees with the recommendation that a clinical study in patients using clinical endpoints should be conducted to support the approval of a generic mesalamine suppository, we do not believe that a placebo arm should be required in all cases as part of the study design.

Use of a 3-arm study including the reference, test and placebo, has the merit of providing a measure of sensitivity for the endpoints being used to evaluate efficacy, thus reducing the risk of a false positive result. However, the use of a placebo in an acute episode of UP should be considered in full respect of the ethical aspect, as the target population for this treatment will require immediate medical care. In addition, it will be all the easier for these patients to have access to approved treatment and hence get the appropriate medical care. This raises significant ethical concerns.

By nature, blinding studies involving suppositories are a challenge, as any coloring agent must be neither more nor less irritating compared to the reference product. Using a double-dummy approach to avoid adding colorant also has its limitations, including potential impact on the compliance of the patients to treatment. In addition, insertion of anything, even just a placebo, into the rectum may affect the mucosa appearance, and can easily irritate an already inflamed mucosa. Consequently, a placebo arm will add significant obstacles in blinding, and could even have some confounding effects on the results.

Axcan appreciates that there may be circumstances where the use of a placebo may be important. This could include, for example, situations where the proposed clinical endpoints have not been previously validated to assess efficacy in UP. However, Axcan urges caution in establishing an inflexible need for a placebo arm in all cases.

2. COMMENTS ON FDA'S SECOND PROPOSED REQUIREMENT

Second FDA Recommended Study(s)	
Type of study:	Bioequivalence studies with pharmacokinetic endpoints (fasting)
Design:	Single-dose, two-way crossover in-vivo
Strengths:	500 mg, 1000 mg, comparing to the respective strengths of the RLD
Subjects:	Normal healthy males and females, general population.
Additional Comments:	Because the 500 mg and 1000 mg strengths are not proportionally similar, a bioequivalence study with clinical endpoints and a bioequivalence study with pharmacokinetic endpoints (fasting) will be needed for each strength product, if you wish to develop each strength.
Analytes to measure (Pharmacokinetic Study):	Mesalamine in plasma
Bioequivalence (Pharmacokinetic Study) based on (90% CI):	Mesalamine

FDA has proposed a conventional pharmacokinetic comparison in healthy volunteers as part of their recommended studies. Axcan does not agree with this proposed study design, and instead believes that systemic exposure to mesalamine in UP patients is more relevant to ensure that a generic mesalamine suppository will be as safe as the RLD.

Although the effectiveness of mesalamine is dependent on local concentrations in the rectal mucosa, it has been hypothesized that systemic circulation of the drug may be associated with side-effects such as acute pancreatitis and nephrotoxicity (French and Mauger, 1993). Since systemic exposure may impact safety, some knowledge of mesalamine absorption is critical in understanding the potential risks of a new formulation. It is Axcan's position that the pharmacokinetics of a new mesalamine rectal formulation should be thoroughly characterized in the target patient population, but that safety should be compared in the clinical study, and not by comparative bioavailability. Using bioequivalence to compare or extrapolate safety would assume that the adverse reactions are solely related to the systemic exposure and this is not the case. It is well known that adverse reactions can be idiosyncratic (and NOT related to extent of systemic exposure) or caused by the excipients that are not taken into account in bioavailability studies. Therefore, relying on plasma concentration rather than on clinical evaluation to assess the comparative safety would be to use an inadequate surrogate marker.

The proposed study in healthy volunteers will not be adequate to reflect maximum exposure levels in patients. As detailed above, the absorption of mesalamine from suppositories is significantly higher in patients with active UP compared to healthy

volunteers and to patients in remission. Therefore, to adequately characterize the pharmacokinetics of a new mesalamine suppository, Axcan believes that systemic exposure in patients with active UP should be evaluated.

3. COMMENTS ON FDA'S PROPOSED DISSOLUTION REQUIREMENTS

In the Draft Guidance, the FDA has proposed dissolution test method and sampling times based on the Dissolution Methods Database. The FDA has requested comparative dissolution testing on 12 dosage units each of all strengths of the test and reference product.

The Draft Guidance further identifies that a Waiver request of *in vivo* testing is not applicable. Axcan agrees with the implied recommendation that *in vitro* testing would be insufficient to prove that a generic product is bioequivalent to the RLD.

For some drug products, *in vitro* dissolution testing alone may be sufficient to demonstrate equivalency of two formulations. FDA has used a Biopharmaceutical Classification System (BCS), which defines circumstances under which a waiver for *in vivo* bioequivalence testing would be possible. To date, this guidance is only applicable to immediate-release solid oral dosage forms, although the Agency is exploring the value of *in vitro* dissolution methods in comparing other types of drug products.

Mesalamine drug products would not be eligible for a waiver for *in vivo* studies using only *in vitro* dissolution testing based on the BCS because:

- Mesalamine does not meet the criteria for high solubility, which is defined as the highest dose strength being soluble in ≤ 250 mL of aqueous media over the pH range of 1-7.5. The intrinsic aqueous solubility is 0.844 g/L (25°C)(French and Mauger, 1993).

- Mesalamine does not meet the criteria for high permeability, which is defined as being a bioavailability of 90% or more. Even when given as an oral tablet, mesalamine bioavailability only reaches 50%. When given as a rectal suppository, bioavailability is estimated to be less than 20%. Therefore, mesalamine would not be considered to be part of Class I high solubility, high permeability drugs for which a waiver for bioequivalence studies would be allowed.

Although mesalamine suppositories have not been specifically developed as a delayed-release dosage form, they also do not exhibit "immediate-release" type characteristics. In order for the active substance to be released from the suppository, the suppository must first melt, and the melting rate controls the drug release rate. The melting point is highly dependent on the excipient type and characteristics, as well as potential drug-excipient interactions.

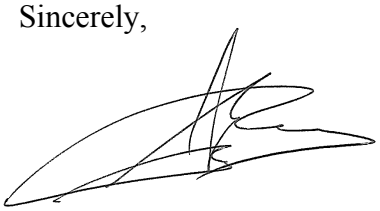
In addition, for mesalamine suppositories, the rectal route of administration complicates extrapolation of *in vitro* dissolution data to what might occur *in vivo*. Unlike dissolution in the stomach, which is a relatively large and aqueous environment, dissolution of the suppository in the rectum is likely to be impacted by small volume and relatively low water content. It is possible that complete dissolution of mesalamine may not be necessary for transport of the active moiety to the lining of the gut wall. In this environment, excipients may play a more important role in interaction with the mucosal cells. In addition, the time of contact between the suppository and the mucosa may be variable due to early expulsion emphasizing the need for *in vivo* data.

The melting of the suppository and subsequent drug release in the small volume of the rectum, as well as any potential local contact of the suppository and excipients with the muscosa, would be very difficult to replicate in an *in vitro* dissolution system based on current knowledge and technologies.

In vitro dissolution of mesalamine suppositories is a component of product quality testing, and is an important criterion for comparing formulations from a quality standpoint. However, *in vitro* dissolution alone would clearly be an inadequate way to prove therapeutic equivalence between two preparations.

In conclusion, on behalf of Axcan Scandipharm, we appreciate the opportunity to comment on the proposed Draft Guidance on Mesalamine. Axcan supports FDA's efforts to develop a product-specific guidance describing data required for an ANDA for mesalamine suppositories. Axcan agrees with the general principles implied by the proposed studies, but, as detailed above, has some specific suggestions for revisions to the draft guidance. We hope that the FDA will consider our suggestions when finalizing this guidance document.

Sincerely,



Dr. Guy Rousseau
Vice President, Regulatory Affairs
Axcan Pharma Inc., Parent Company of Axcan Scandipharm, Inc.
22 Inverness Center Pkwy,
Birmingham, Alabama, 35242
(Ph) 205-991-8085
(Fax) 205-991-9547

CITED REFERENCES

Aumais G, Lefebvre M, Tremblay C, Bitton A, Martin F *et al.* Rectal tissue, plasma and urine concentrations of mesalazine after single and multiple administrations of 500 mg suppositories to healthy volunteers and ulcerative proctitis patients. Ailment Pharmacol Ther 2003;17:93-97.

Bondesen S, Schou JB, Pedersen V, Rafiolsadat Z, Hansen SH *et al.* Absorption of 5-ASA from colon and rectum. Br J Clin Pharmacol 1988;25:269-272.

Campieri M, Lanfranchi GA, Boschi S, Brignola C, Bazzocchi G *et al.* Topical administration of 5-ASA enemas in patients with ulcerative colitis. Studies on rectal absorption and excretion. Gut 1985;26:400-405.

CANASA® Rectal Suppositories Package Insert.

Christensen, LA. 5-ASA containing drugs. Delivery, fate, and possible clinical implications in man. Danish Med Bull 2000;47:20-38.

Cohen RD, Woseth DM, Thisted RA, Hanauer SB. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. Am J Gastroenterol. 2000;95:1263-1276.

d'Albasio G, Pacini F, Camarri E, Messori A, Trallori G *et al.* Combined therapy with 5-ASA tablets and enemas for maintaining remission in ulcerative colitits: a randomized double-blind study. Am J Gastroenterol. 1997:92:1143-1147.

Dietrich CG, Geier A, Oude Elferink RPJ. ABC of oral bioavailability: transporters as gatekeepers in the gut. Gut 2003;52:1788-1795.

Food and Drug Administration. Draft Guidances for Industry Describing Product-Specific Bioequivalence Recommendations; Availability Notice. 72 FR 30386.

FDA Guidance for Industry. Bioequivalence recommendations for specific products. May 2007 OGD

FDA Guidance for Industry. Draft Guidance on Mesalamine. May 2007 OGD

FDA Guidance for Industry. Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. August 2000.

Fischer C, Maier K, Klotz, U. Simplified high performance chromatographic method for 5-aminosalycylic acid in plasma and urine. J Chromatogr 1981;222:498-503.

French DL, Mauger JW. Evaluation of the physicochemical properties and dissolution characteristics of mesalamine: relevance to controlled intestinal drug delivery. Pharm Res 1993;10:1285-1290.

Frieri G, Giacomelli R, Pimbo M, Palumbo G, Passacantando A *et al.* Mucosal 5-aminosalicylic acid concentrations inversely correlates with severity of colonic inflammation in patients with ulcerative colitis. Gut 2000;47:410-414.

Frieri G, Pimpo MT, Palumbo GC, Onori L, Viscido A *et al.* Rectal and colonic mesalazine concentration in ulcerative colitis: oral vs. oral plus topical treatment. Ailment Pharmacol Ther 1999;13:1413-1417.

Jacobsen BA, Abildgaard K, Rasmussen HH, Christensen LA, Fallingborg J *et al.* Availability of mesalazine (5-ASA) from enemas and suppositories during steady-state conditions. Scand J Gastroenterol 1991;26:374-378.

Klotz U. Clinical pharmacokinetics of sulphasalazine, its metabolites and other prodrugs of 5-ASA. Clin Pharmacokinet 1985;10:285-302.

Norlander B, Gotthard R, Strom M. Pharmacokinetics of a 5-ASA enteric-coated tablet and suppository dosage form. Ailment Pharmacol Therap 1989;3:333-342.

Safdi M, DeMicco M, Sninsky C, Banks P, Wruble L *et al.* A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. Am J Gastroenterol 1997:92:1867-1871.

Williams CN, Haber G, Aquino JA. Double-blind, placebo-controlled evaluation of 5-ASA suppositories in active distal proctitis and measurement of extent of spread using ^{99m}Tc-labeled 5-ASA suppositories. Dig Dis Sci 1987;32:71S-75S.